Early treatment with captopril after acute myocardial infarction

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Abstract

***Objectives*—To determine the effects of early treatment with captopril on haemodynamic function, neuroendocrine biochemistry, left ventricular structure, clinical outcome, and exercise capacity over one year from acute myocardial infarction.**

***Design*—Randomised, double blind, placebo controlled comparison of captopril and placebo.**

***Setting*—Coronary care units and cardiology departments of two university teaching hospitals in Glasgow.**

***Patients*—99 haemodynamically stable patients with acute myocardial infarction, selected on clinical grounds as being at risk of late ventricular dilatation.**

***Intervention*—Captopril or identical placebo started between six and 24 hours after start of symptoms and continued for 12 months. Target maintenance dose was 25 mg three times a day.**

***Main outcome measures*—(*a*) Acute haemodynamic effects of treatment; (*b*) neuroendocrine biochemistry from admission to two months; and (*c*) change in echocardiographic measures of left ventricular size, clinical outcome, and exercise capacity after 12 months of treatment with a separate analysis of the effects of one month of treatment withdrawal on left ventricular volumes.**

***Results*—Captopril caused acute reductions in mean (SEM) pulmonary artery pressure (2·48 (0·69) mm Hg) and systemic vascular resistance (260 (103)) dyn. s. cm^{-5}). Over the first 10 hours captopril reduced mean arterial pressure by 12·1 (2·4) mm Hg compared with 3·8 (1·9) mm Hg in the placebo group. No patient had to be withdrawn from the captopril group because of hypotension. From day 1 onwards systolic and diastolic arterial pressures in the captopril treated group were slightly but not significantly lower than on placebo. There was no difference in the incidence of ventricular or supraventricular arrhythmia with treatment. Captopril prevented the day 3 peak in angiotensin II that occurred in the placebo group (peak concentration (interquartile range): 10·1 (4·8–19·4) pg/ml *v* 16·8 (4·3–46·3) pg/ml)) but had no effect on atrial natriuretic factor, arginine vasopressin, or catecholamines. Plasma atrial natriuretic factor remained above normal in both groups at two months after infarction. After one year left ventricular volume indices had increased less on captopril than on placebo: left ventricular end systolic volume index 5·4 ml/m^2 *v* 14·7 ml/m^2 (95% confidence interval (95% CI) of difference −14·6 to −3·9; p=0·0011); left ventricular end diastolic volume index 8·4 ml/m^2 *v* 19·0 ml/m^2 (95% CI of difference, −17·0 to −4·2; p=0·0016). Withdrawal of captopril for one month did not affect ventricular volumes. There was no difference in exercise capacity.**

***Conclusions*—Captopril started between six and 24 hours after acute myocardial infarction is not associated with significant hypotension. It suppresses activation of the renin angiotensin system but has no effect on plasma concentrations of other neurohormones. Atrial natriuretic factor remains raised at two months after myocardial infarction. Captopril significantly decreases left ventricular dilatation. This effect is not lost after one month of treatment withdrawal and is thus due to an alteration of left ventricular structure and not to a short lived haemodynamic action of captopril. Long-term treatment with captopril does not result in improved aerobic exercise capacity after acute myocardial infarction.**

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Significant left ventricular dilatation occurs in 20%-25% of patients with acute transmural myocardial infarction.[1 2] Ventricular enlargement is associated with the development of cardiac failure and an adverse prognosis.[3 4] Treatment strategies that limit progressive ventricular remodelling have the potential to lessen the incidence of late cardiac failure and death. Captopril started a week or more after the infarction limits left ventricular enlargement.[5 6] Experimental and clinical evidence suggests that the process of left ventricular dilatation begins early after transmural myocardial necrosis and develops rapidly in the first few days at a time when the renin angiotensin system is activated.[5 7-9] Prompt intervention with captopril may attenuate this early rapid phase of left ventricular dilatation and maximise its beneficial effects on left ventricular function. The aim of this study was to examine the acute haemodynamic effects of captopril started within 24 hours of acute myocardial infarction and to determine its

long-term actions on neuroendocrine biochemistry, left ventricular structure, clinical outcome, and exercise capacity. A preliminary analysis of the early effects of captopril on left ventricular remodelling in these patients has been the subject of a separate report.[10]

Patients and methods

This was a two centre double blind placebo controlled comparison of captopril and placebo started within 24 hours of acute myocardial infarction. The study protocol was approved by the ethics committees of both institutions and all patients gave informed consent. We recruited 99 clinically and haemodynamically stable patients (82 men 17 women) aged 40–75 years and admitted within 24 hours of the start of chest pain. Electrocardiographic requirements for entry were ST elevation of at least 3 mm in 2 precordial leads V1-V4 or 2 mm in two frontal plane leads or V5-6 or any ST elevation in two frontal plane leads with ST depression compatible with posterior wall infarction of at least 3 mm in two precordial leads. To avoid recruiting patients with small infarcts and at low risk of ventricular dilatation we excluded those with a Norris score <3·5.[11] Other exclusion criteria were systolic blood pressure < 95 mm Hg on admission, history of significant renal or cerebrovascular disease, contraindications to captopril, or a definite indication for its use and inability to give informed consent. At the time of recruitment into this study, the policy in our coronary care units was not to give thrombolytic treatment to patients seen six or more hours after the start of symptoms. These patients, plus those in whom contraindications to thrombolytic treatment existed, were eligible for recruitment into our study. After randomisation and baseline investigations patients received 6·25 mg of the trial medication, which if tolerated was repeated at one hour. At eight hours 12·5 mg was given then 12·5 mg three times daily with a target dose of 25 mg three times daily before discharge from hospital. If the systolic blood pressure was persistently less than 85 mm Hg the next scheduled dose was omitted and the subsequent dose halved. If despite dose reduction systolic blood pressure remained persistently less than 85 mm Hg the patient was withdrawn from the study. Other withdrawal criteria were serum urea >20 mmol/l despite dose reduction, development of cardiac failure requiring open label captopril or any condition defined previously as an exclusion criterion, or a severe adverse drug effect thought to be related to captopril. All medications except angiotensin converting enzyme inhibitors could be given at the discretion of the individual physician. Table 1 shows the baseline characteristics of the treatment groups.

CLINICAL FOLLOW UP

Patients underwent a detailed clinical assessment on admission and on days 1, 2, 3, and 7 to 10 and at one, two, four, six, nine, and 12 months when trial medication was withdrawn. A further assessment was made at 13 months, one month after withdrawal from treatment. In one centre 41 patients had 7F thermodilution Swan Ganz catheters inserted through the internal jugular or brachiocephalic veins to record cardiac filling pressures and cardiac output before and after the first two doses of captopril. All measurements were made in triplicate in end expiration. For the first 72 hours after admission heart rate and rhythm were monitored continuously on a central console. Holter recorders were attached for 24 hours after admission and immediately before discharge from hospital for detailed analysis of arrhythmias. Continuous wave Doppler echocardiography was performed at baseline, at day 3, and at days 7-10. The cardiac index was derived from standard formulae.[12]

NEUROENDOCRINE DATA

Before the first dose of trial medication an indwelling forearm cannula was inserted and after 30 minutes supine rest venous blood was drawn for assay of atrial natriuretic factor, renin, angiotensin II, arginine vasopressin, adrenaline, and noradrenaline. Sampling was repeated by the same technique at day 3, days seven to 10, and at two months. At all time points from admission sampling was performed about two hours after the last dose of trial medication. All assays were performed in the laboratories of the Medical Research Council Blood Pressure Unit with previously described techniques.[13–17] Normal ranges are: atrial natriuretic factor 5–50 pg/ml; renin 9–50 μu/ml; angiotensin II <20 pg/ml, arginine vasopressin 0·3–0·7 pg/ml; adrenaline <1 nmol/l; noradrenaline <5 nmol/l.

ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed on days 1, 3, and 7 to 10 and at one, two, six, 12, and 13 months. Three experienced echocardiographers obtained all the ultrasound data. A short axis parasternal view of the left ventricle at the level of the tips of the papillary muscles in end diastole was used to measure anterior and posterior endocardial segment lengths as previously described.[18] Left ventricular volumes were calculated in one centre by the method of Tortoledo *et al*[19] and in the other by a 10 segment Simpson's rule method.[20] Patient and transducer positions were recorded at the initial scan and maintained between successive examinations. All measurements were averaged over three consecutive cardiac cycles. All images for an individual patient were acquired and analysed by the same operator. Day to day intraobserver variability was determined from a random sample of 30 patients (10 for each operator) examined twice within a 48 hour period at the end of the study.[21] Each of these scans was recorded on a separate video tape, coded, and analysed blind at the end of the study. The SDs of repeated measurements were: left

ventricular end diastolic volume index 6·1 ml/m², left ventricular end systolic volume index 6·2 ml/m², anterior segment length 5 mm, posterior segment length 5 mm. A change within any individual patient that was greater than two SDs of the measurement error was considered significant.

EXERCISE TESTS

Before discharge treadmill exercise testing was undertaken on a modified Bruce protocol limited to nine minutes. Symptom limited cardiopulmonary exercise testing on a Bruce protocol was performed at 12 and 13 months. Respiratory variables were measured on a Beckman metabolic measurement chart (Horizon).

STATISTICAL ANALYSIS

The study was analysed on a limited intention to treat basis with all available patients at each time point. A separate analysis was performed comparing one year and 13 months to determine the effects of withdrawal from treatment. Categorical variables were analysed with the χ^2 or Fisher's exact tests and continuous variables with unpaired Student's t test incorporating the Aspin-Welch modification or the Mann-Whitney U test. The Bonferroni correction was used as appropriate to allow for multiple comparisons.[22] Data are expressed as mean (SEM) except for the neuroendocrine data, which are expressed as median and interquartile range.

Results

CLINICAL OUTCOMES

At baseline the two treatment groups were well matched except for an inequality in the distribution of patients with a previous myocardial infarction (table 1). Over one year of follow up there were eight deaths (four sudden) in the captopril group and 10 (six sudden) in the placebo group. Thirteen of these patients died within two months of infarction. All five deaths between two months and one year were in the placebo group. Table 2 shows only twenty two patients were withdrawn from the study medication. Seventy three patients were available for analysis at the end of the study including 14 patients who had been withdrawn from the study medication but who had continued blinded follow up. There was no difference in the use of non-trial cardiac drugs at one year.

HAEMODYNAMIC FUNCTION

At baseline cardiac filling pressures tended to be higher and cardiac output lower in the captopril group (table 1). Over the 10 hour period from initial dosing captopril caused a significantly greater fall in mean arterial pressure than did placebo (fig 1). The fall in blood pressure in the captopril group was not associated with a rise in heart rate (fig 2). There was no relation between the fall in mean arterial pressure and the admission concentration of angiotensin II. At two hours there had been small but significant falls in mean pulmonary artery pressure and systemic vascular resistance in the captopril group compared with small rises in the placebo group (table 3), but no increase in cardiac output. From day 1 both systolic and diastolic blood pressure in the captopril group remained slightly but not significantly lower than in the placebo group (table 4). There was no significant difference in cardiac index by Doppler ultrasound between the treatment groups (fig 3).

Table 1 Baseline characteristics

	Captopril (n = 49)	*Placebo (n = 50)*
Age (yr)	61 (1)	59 (1)
Sex (M/F)	40/9	42/8
Previous AMI	2	13*
Peak CK (IU)	2887 (318)	2334 (242)
Killip class 1	32	31
2	14	19
3	3	0
Norris index	6·2 (0·2)	6·3 (0·2)
Infarct site:		
Anterior	28	31
Inferoposterior	21	19
Time to start of treatment (h)	14·3 (1·0)	16·6 (0·9)
Heart rate	78 (3)	83 (2)
Systolic BP	133 (3)	131 (4)
Diastolic BP	86 (2)	83 (2)
RAP	8·4 (0·9)	7·3 (0·6)
PAMP	25·2 (1·6)	22·0 (1·3)
PAWP	15·8(1·5)	13·9 (1·3)
CO (l/min)	4·26 (0·32)	4·6 (0·24)
SVR (dyn.s.cm^{-5})	1891 (136)	1610 (127)
LVESVI (ml/m²)	42·7 (2·2)	47·3 (2·2)
LVEDVI (ml/m²)	67·7 (2·5)	72·5 (2·1)
SVI (ml/m²)	25·0 (1·4)	25·2 (1·3)
EF%	37·4 (1·8)	35·2 (1·8)

*p = 0·002. AMI, acute myocardial infarction; CK, creatine kinase; BP, blood pressure: RAP, right atrial pressure; PAMP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; SVR, systemic vascular resistance (invasive haemodynamics are for 41 patients only); LVESVI, left ventricular end diastolic volume index; SVI, stroke volume index; EF, ejection fraction. Values are mean (SEM) where applicable.

Table 2 Reasons for withdrawal

	Captopril	*Placebo*
Cardiac failure	2	2
Reinfarction	3	1
Unstable angina	0	3
CABG	1	1
LV aneurysmectomy	1	0
Hypotension	0	1
Cough	1	0
Non-compliance	2	1
Other illness	2	1

LV, left ventricular; CABG, coronary artery bypass grafting

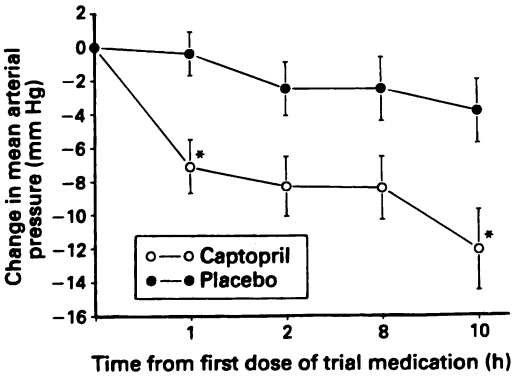

*Figure 1 Change in mean (SEM) arterial pressure from baseline. *p < 0·05.*

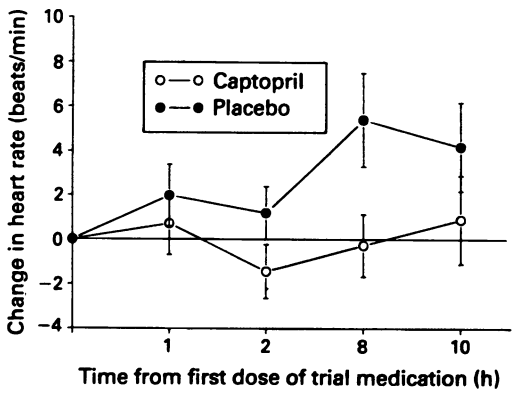

Figure 2 Change in mean (SEM) heart rate from baseline.

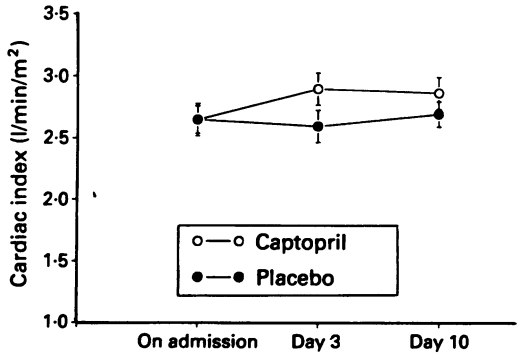

Figure 3 Mean (SEM) cardiac index by Doppler ultrasound.

ARRHYTHMIAS

There was no difference in the incidence of ventricular or supraventricular arrhythmias between the treatment groups either after admission or before discharge.

NEUROENDOCRINE RESPONSES

Pretreatment concentrations of all hormones except adrenaline tended to be higher in the captopril group (table 5). In the placebo group concentrations of renin and angiotensin II rose from admission to day 3. This trend was present even in those patients not treated with diuretics. In this subgroup median plasma renin concentrations rose from 27 μu/ml on admission to 64 μu/ml at day 3, and fell to 39 μu/ml at days 7–10. Corresponding angiotensin II concentrations were 11·0 pg/ml, 13·6 pg/ml, and 8·7 pg/ml. Captopril caused a considerable increase in renin concentration and suppressed the rise in angiotensin II seen in the placebo group. Plasma atrial natriuretic factor peaked at three days in both treatment groups, and remained above normal throughout the study irrespective of treatment. Plasma concentrations of catecholamines and arginine vasopressin were also unaffected by treatment.

Table 3 Change in invasive haemodynamics from baseline to two hours

	Captopril (n = 21) Mean (SEM)	*Placebo (n = 20) Mean (SEM)*
RAP mm Hg	− 0·92 (0·82)	1·55 (1·7)
PAMP mm Hg	− 2·48 (0·69)**	0·75 (0·77)
PAWP mm Hg	− 1·91 (1·0)	1·18 (1·5)
CO l/min	− 0·06 (0·08)	− 0·13 (0·17)
SVR dyn.s.cm^{-5}	− 260 (103)*	72 (54)

*p < 005, **p < 0·01.
RAP, right atrial pressure; PAMP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output, SVR, systemic vascular resistance.

Table 4 Serial heart rates and blood pressures from baseline to 13 months

	Baseline	*Day 1*	*Day 3*	*Days 7–10*	*Two months*	*One yr*
			Captopril			
HR	78 (3)	80 (3)	80 (3)	75 (2)	70 (2)	64 (3)
SBP	133 (3)	115 (3)	109 (2)	108 (2)	121 (3)	127 (4)
DBP	86 (2)	74 (2)	70 (2)	68 (1)	74 (2)	67 (3)
			Placebo			
HR	83 (3)	85 (2)	82 (2)	76 (2)	72 (2)	67 (3)
SBP	131 (4)	124 (3)	109 (2)	111 (2)	121 (3)	132 (5)
DBP	83 (2)	79 (2)	73 (1)	72 (1)	78 (2)	83 (3)

HR, heart rate (beats/min); SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg).

ECHOCARDIOGRAPHY

At baseline there was a trend towards higher mean indices of left ventricular volume in the placebo group consistent with the greater incidence of previous infarcts (table 1). Table 6 shows the changes in echocardiographic indices from admission to one year in patients with analysable images. In both anterior and inferoposterior infarcts captopril limited the expansion of the endocardial segment containing the infarct that is the anterior segment in the anterior infarcts and the posterior segment in the inferoposterior infarcts (fig 4). This effect was less pronounced in the segments not containing an infarct. Ventricular dilatation was attenuated in the captopril group. At one year mean end systolic volume index was 47·0 (2·8) ml/m^2 in the captopril group and 59·9 (3·4) ml/m^2 in the placebo group ($p = 0.005$, fig 5). Corresponding figures for mean end diastolic volume index were 76·9 (3·0) ml/m^2 and 89·4 (3·1) ml/m^2 ($p = 0.005$, fig 6). Five of 30 patients in the captopril group developed an increase in left ventricular end systolic volume index > 2 SDs of the measurement error compared with 15 of 31 in the placebo group ($p = 0.001$). The corresponding rates for end diastolic volume index were six of 30 in the captopril group and 19 of 31 in the placebo group ($p < 0·001$). Excluding those patients with a previous infarct made no substantial difference to these results (table 6). The effects of captopril on ventricular remodelling were, however, less noticeable in patients with inferior infarcts. Withdrawal of treatment for one month had no effect on left ventricular volumes (figs 5 and 6).

EXERCISE VARIABLES

At the exercise test before discharge there was no difference in the occurrence of exercise induced ischaemia. Data on cardiopulmonary exercise testing at one year were available in 67 patients. There was no difference between the treatment groups in any variable (table 7). The exclusion of those patients with evidence of exercise induced ischaemia did not influ-

Table 5 Serial hormone concentrations by treatment group

	Captopril				*Placebo*			
	Baseline	*Day 3*	*Days 7–10*	*Two months*	*Baseline*	*Day 3*	*Days 7–10*	*Two months*
Renin (μul/ml)	31 (14–56)	137* (65–294)	112** (54–189)	61* (30–110)	22 (16–85)	67 (24–169)	42 (14–75)	20·5 (12–48)
AII (pg/ml)	15·6 (4·4–27·5)	10·1* (4·8–19·4)	5·2* (2·4–8·1)	3·3** (2·0–5·8)	12 (5·8–27·4)	16·8 (7·3–46·3)	8·1 (5·1–19·0)	6·1 (4·0–14·9)
ANF (pg/ml)	72 (49–100)	99·5 (50–133)	78 (46–124)	58 (42–84)	60 (40–85)	74 (48–122)	68·5 (35–100)	58 (35–94)
ADR (nmol/l)	0·6 (0·4–1·2)	0·3 (0·1–0·6)	0·2 (0·1–0·2)	0·2 (0·1–0·3)	0·6 (0·4–0·3)	0·2 (0·1–0·3)	0·2 (0·1–0·2)	0·2 (0·1–0·2)
NADR (nmol/l)	4·8 (3·6–6·8)	3·4 (2·3–5·0)	2·4 (1·8–3·6)	2·6 (2·1–3·6)	4·3 (2·7–6·8)	3·0 (2·4–5·4)	1·9 (1·4–3·4)	4·1 (1·8–4·8)
AVP(pg/ml)	4·63 (2·1–16·0)	0·99 0·4–1·9)	0·45 (0·3–0·9)	0·47 (0·2–1·1)	3·22 (0·8–7·2)	1·29 (0·6–3·1)	0·49 (0·2–0·9)	0·72 (0·2–1·7)

*p < 0·05; **p < 0·01.
AII, angiotensin II; ANF, atrial natriuretic factor; ADR, adrenaline; NADR, noradrenaline; AVP, arginine vasopressin. Concentrations are median and interquartile range.

Table 6 Change in echocardiographic variables from admission to one year

	Captopril	*Placebo*	*(95% CI of difference)*	*p Value*
Infarct segment (mm):				
Ant MI	n = 13	n = 16		
	4·3 (2·6)	16·9 (3·6)	(− 21·7 to − 3·5)	0·009
Inf MI	n = 12	n = 10		
	4·3 (2·4)	13·5 (2·8)	(− 17·7 to − 0·8)	0·033
Non-infarct segment (mm):				
Ant MI	n = 13	n = 16		
	3·8 (2·2)	7·0 (3·5)	(− 11·6 to 5·2)	0·43
Inf MI	n = 12	n = 10		
	6·1 (2·2)	14·6 (4·4)	(− 19·2 to 2·2)	0·11
Left ventricular volumes (ml/m²):				
All patients	n = 30	n = 31		
LVEDVI	8·4 (1·9)	19·0 (2·6)	(− 17·0 to − 4·2)	0·0016
LVESVI	5·4 (1·3)	14·7 (2·3)	(− 14·6 to − 3·9)	0·0011
SVI	3·0 (1·2)	4·3 (1·5)	(− 2·5 to 5·2)	0·48
EF%	− 0·1 (1·2)	− 1·9 (1·7)	(− 2·5 to 6·0)	0·41
Ant MI	n = 17	n = 20		
LVEDVI	9·2 (2·3)	21·3 (3·0)	(− 19·8 to − 4·3)	0·0015
LVESVI	6·3 (1·7)	16·3 (2·9)	(− 16·8 to − 3·2)	0·0054
SVI	2·9 (1·3)	4·9 (2·0)	(− 2·8 to 6·9)	0·40
EF%	− 0·9 (1·4)	− 0·7 (2·4)	(− 5·9 to 5·4)	0·93
Inf MI	n = 13	n = 11		
LVEDVI	7·3 (3·1)	14·8 (4·7)	(− 19·4 to 4·4)	0·20
LVESVI	4·2 (2·1)	11·6 (3·9)	(− 16·9 to 2·1)	0·12
SVI	3·1 (2·2)	3·2 (2·2)	(− 6·3 to 6·5)	0·97
EF%	1·1 (2·2)	− 3·9 (2·3)	(− 1·6 to 11·6)	0·13
First MI only	n = 29	n = 24		
LVEDVI	8·3 (1·9)	20·9 (3·1)	(− 20·1 to − 5·2)	0·0015
LVESVI	5·3 (1·4)	16·7 (2·7)	(− 17·5 to − 5·3)	0·0005
SVI	3·0 (1·2)	4·2 (1·6)	(− 2·8 to 5·2)	0·55
EF%	0·1 (1·3)	− 2·4 (1·8)	(− 1·9 to 6·9)	0·26

Ant MI, anterior myocardial infarction; Inf MI, inferoposterior myocardial infarction. Other abbreviations as for table 1. Captopril and placebo values are mean (SEM).

ence the results. Exercise capacity did not correlate with resting left ventricular volumes or ejection fraction. Withdrawal of treatment for one month had no significant effect on any exercise variable.

Discussion

In this study we have shown that captopril can be started safely within 24 hours of acute myocardial infarction in a population of patients at risk of progressive ventricular dilatation. To minimise the potential risks of hypotension we included only patients who were haemodynamically stable six hours after the start of chest pain. In the light of initial adverse reports about the combined use of captopril and streptokinase[23] we elected to exclude streptokinase treated patients from the study. The study was started before the results of the Second International Study of Infarct Survival Trial were published,[24] when the upper time limit for the use of streptokinase in our institutions was six hours, and before tissue plasminogen activator was readily available for routine use. Several small studies have shown that captopril is effective in treating left ventricular failure early after myocardial infarction[25–27] but our trial is the first to examine targeted prophylactic captopril treatment in the period immediately after infarct. If acute captopril treatment is to gain acceptance as a measure to prevent late ventricular dilatation it must be free of significant side effects particularly during the acute dose period and the in hospital phase. With an incremental dose regimen we were able to introduce captopril without significant hypotension and with no evidence for clinically relevant aggravation of myocardial ischaemia either during the acute dose period or at the exercise test before discharge. Only two patients with a previous infarct were randomised to the captopril treatment and it is conceivable that hypotension might have been more apparent had there been more patients with a previous infarct in the capto-

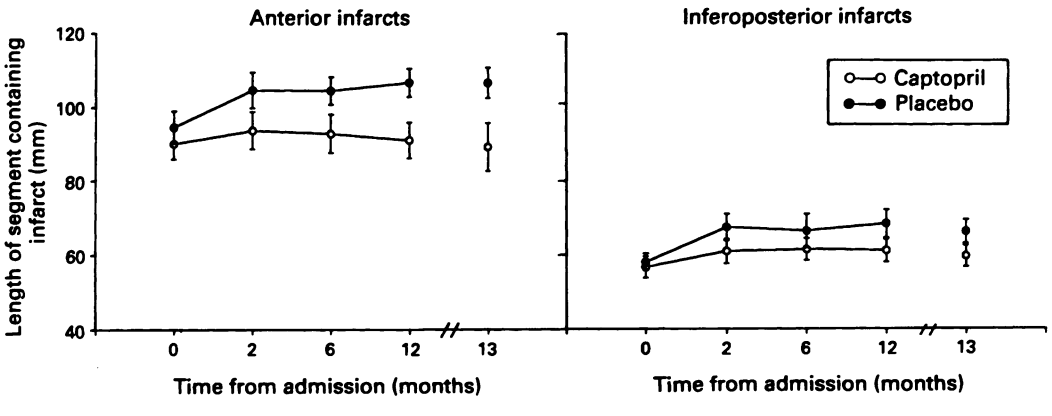

Figure 4 Mean (SEM) change in length of segment containing infarct from admission to 12 months.

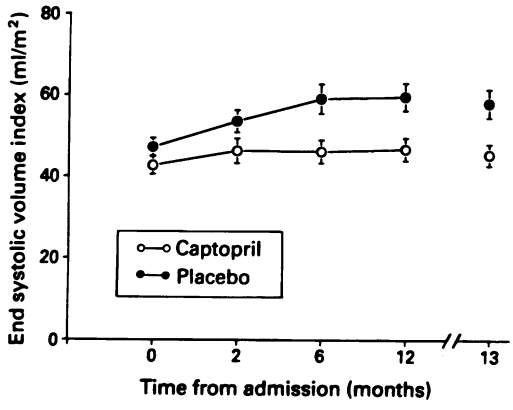

Figure 5 Mean (SEM) left ventricular end systolic volume index from admission to 12 months and after one month after withdrawal from treatment.

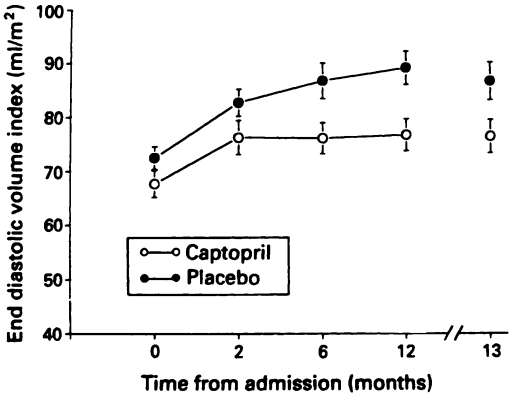

Figure 6 Mean (SEM) left ventricular end diastolic volume index from admission to 12 months and after one month after withdrawal from treatment.

pril treated group. The immediate effects of captopril on cardiac filling pressures in this study are similar to those found in smaller studies of patients with postinfarction cardiac failure where similar dose schedules have been used.[25 26] Despite acute vasodilatation captopril did not increase cardiac output either acutely or in the early convalescent phase.

The tendency to a greater degree of neuroendocrine activation in the captopril group at baseline is consistent with the trend to higher cardiac filling pressures and a higher peak creatine kinase in these patients. We have confirmed previous findings of stimulation of the renin angiotensin system three days after acute myocardial infarction even in the absence of diuretic treatment[9]. The mechanism for this effect remains uncertain but it may be related to increased sympathetic outflow to the renal nerves and hence increased renin secretion.[28] Captopril prevented the rise in concentrations of angiotensin II at day three and, compared with placebo, concentrations remained depressed at two months. As well as its potent vasoconstrictor and antinatriuretic actions, angiotensin II is cardiotoxic[29 30] and raised concentrations in the immediate aftermath of myocardial infarction may be particularly deleterious. The prompt use of an angiotensin converting enzyme inhibitor should minimise these harmful effects.

Table 7 Cardiopulmonary exercise testing at one year

	Captopril (n = 35) Mean (SEM)	*Placebo (n = 32) Mean (SEM)*
Exercise time (s)	448 (36)	435 (31)
Peak HR	138 (4·1)	135 (4·3)
Peak SBP (mm Hg)	163 (4·2)	167 (4·6)
V_{O_2} max (ml/kg/m²)	23·1 (1·1)	22·2 (1·0)
V_{CO_2} max (ml/kg/m²)	22·4 (1·3)	22·7 (1·3)
VE (l/min)	59·1 (3·5)	62·6 (3·5)
RER	1·030 (0·028)	1·026 (0·022)
ST> − 1 mm	11	9
Time to ST − 1 mm (s)	330 (46)	327 (58)

V_{O_2}, oxygen uptake; V_{CO_2}, carbon dioxide output; VE, ventilation; RER, respiratory exchange ratio; ST> − 1, number of patients developing >1 mm of ST elevation. Other abbreviations as for table 4.

We have confirmed the occurrence of a peak in plasma atrial natriuretic factor two to four days after infarction.[30 31] Previous studies have found concentrations of plasma atrial natriuretic factor to be raised for up to 15 days,[32] but a persistent increased concentration over two months after acute myocardial infarction has not previously been reported and presumably reflects persistent left ventricular dysfunction (left ventricular ejection fractions at two months were 40·4% (2·0%) in the captopril group and 36% (1·2%) in the placebo group). Chronic captopril treatment after acute myocardial infarction both lowers cardiac filling pressures and improves left ventricular function[5 6] and would thus be expected to lower plasma concentrations of atrial natriuretic factor. Previous studies have been contradictory. McAlpine *et al* found that acute doses of captopril in patients with acute left ventricular failure had no consistent effects on atrial natriuretic factor despite a significant fall in both right atrial and pulmonary capillary wedge pressures[33]. In patients with chronic stable heart failure Rouleau *et al* noted an acute fall in plasma concentrations after the initial dose but after one month of treatment concentrations were similar to those at baseline.[34] These findings suggest that captopril might modify the release of atrial natriuretic factor such that secretion is increased for a given degree of atrial distension and is less sensitive to a fall in atrial pressure. This hypothesis, however, is not supported by the results of other studies. Swedberg *et al* found a 20% fall in concentrations of atrial natriuretic factor after six weeks of enalapril treatment in patients with severe chronic heart failure.[35] In acute dose studies in salt replete normal volunteers captopril has either no effect,[36] or increases circulating concentrations of atrial natriuretic factor.[37] In salt depleted patients with an activated renin angiotensin system enalapril reduces concentrations acutely.[38] In the light of these conflicting results it is likely that the interaction between atrial natriuretic factor and inhibition of angiotensin converting enzyme is complex. It is possible that in patients with a considerably activated renin angiotensin system the vasodilator action of converting enzyme inhibition is predominant, resulting in a fall in atrial distension and thus a fall in circulating atrial natriuretic factor. In subjects with a lesser degree of activation of the renin angiotensin system the haemody-

namic effects of converting enzyme inhibition are less noticeable and modification of secretion could predominate. If this is the case then this may be an advantage for converting enzyme inhibitors over other vasodilators.

Concentrations of arginine vasopressin in this study are similar to those described previously.[9] In patients with stable heart failure long-term captopril treatment leads to a reduction in arginine vasopressin[39] but there is no effect with short term treatment either in stable heart failure[40] or in acute left ventricular failure where concentrations are noticeably increased.[33] In acute and chronic heart failure the effects of converting enzyme inhibition on catecholamines have been variable with either no effect[33 40] or a decrease in noradrenaline.[27 41] At the time of entry to the present study median concentrations of both adrenaline and noradrenaline were in the upper reaches of the normal range and it would have been surprising had any effect of captopril been seen. The initial fall, however, in arterial pressure in the captopril group in the absence of a compensatory tachycardia provides indirect evidence of a sympatholytic effect.

We have shown that oral captopril started within 24 hours of symptoms greatly reduces left ventricular remodelling over the first year after acute myocardial infarction. Left ventricular dilatation begins within hours of transmural myocardial necrosis and is particularly rapid over the first 10–14 days.[5 7 8] At one week after infarction left ventricular end systolic volume index is already 85% above normal and left ventricular end diastolic volume index 35% above normal.[5] Sharpe *et al* found that captopril started at a mean of nine days after infarction and continued for a year caused a significant reduction in left ventricular end systolic volume index and an increase in stroke volume index from baseline.[5] In a second study the same authors randomised patients to captopril or placebo at 24–48 hours after admission and followed them up for three months.[42] Early captopril treatment prevented much of the dilatation present at baseline in their original study. It is not possible to draw a direct comparison with our study as we included patients with more severe degrees of left ventricular impairment. We started captopril at a mean of 15 hours from symptoms in a population of patients selected on simple clinical grounds alone as being at risk of progressive left ventricular dilatation. Preliminary results from other studies suggest that it is safe to start angiotensin converting enzyme inhibition at an even earlier stage after infarction, though the benefits of this approach are not yet clear.

Thirteen of the 15 patients with a previous infarct were randomised to placebo. To account for this inequality we reanalysed our data to include only those patients with a first myocardial infarction and this made no significant difference to the overall findings. Second infarcts cause less remodelling than first infarcts[43] and the uneven distribution would if anything have tended to reduce the extent of ventricular enlargement from baseline in the placebo group. We deliberately selected patients at risk of ventricular dilatation. About 40% of the total increase in left ventricular volumes in our placebo patients occurred in the first 10 days after infarction but chamber dilatation continued over the course of the study. Similar persistence of ventricular dilatation has been found in other studies.[1 44] The optimal duration of captopril treatment remains to be defined but our results suggest that it should be continued for at least a year and possibly indefinitely. The lack of a change in ventricular volumes in the captopril group after the month of treatment withdrawal confirms that the reduction in ventricular dilatation is structural and not due simply to a rapidly reversible haemodynamic effect. It does not allow us to determine the mechanism underlying the effect of captopril.

None of the patients in our study received thrombolytic treatment. Thrombolysis and a patent infarct related artery reduce the extent of ventricular remodelling[44 45] but captopril is none the less effective in attenuating ventricular dilatation in patients treated with streptokinase[46] and probably in those treated with tissue plasminogen activator.[47] A significant proportion of patients with acute myocardial infarction have either contraindications to the use of thrombolytics, present too late for effective thrombolysis, or fail to reperfuse. These are the patients who probably have most to gain from treatment with captopril.

We were unable to show any benefit of captopril treatment on aerobic exercise capacity and there was no correlation between exercise capacity and resting left ventricular function. Captopril improves exercise capacity in patients with congestive cardiac failure[48] but few of our patients fell into this category. In both treatment groups maximal oxygen uptake was in the low normal range.[49] By contrast Pfeffer *et al* found exercise time to be significantly prolonged in captopril treated patients but included only those who did not develop exercise induced ischaemia.[6] To allow a better comparison we reanalysed our data to exclude patients developing exercise induced ischaemia but this had no material effect on the outcome.

Our study indicates that captopril treatment within 24 hours of acute myocardial infarction is a practical strategy to limit progressive left ventricular dilatation in high risk patients identified on simple clinical grounds alone. Withdrawal of captopril did not lead to a rapid reversal of these changes implying that they have a structural basis. The eventual place of angiotensin converting enzyme inhibition in the management of myocardial infarction will be dependent on evidence that their beneficial effects on remodelling are converted long-term into a reduction in mortality and improved functional state. Although the Consensus 2 Study failed to show a reduction in mortality with enalapril[50] the initial results of the SAVE (Survival and Ventricular Enlargement Study) show that captopril reduced both cardiovascular mortal-

ity and progression to cardiac failure when started between three and 16 days after infarction in patients with an ejection fraction below 40%.[51]

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